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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

31397 U.S. PTO
06815933
03/13/97

Docket No. DAVCO-42430

Anticipated Classification of this application:

Class _____ Subclass _____

Prior application:

Examiner N. Johnson

Art Unit 1806

BOX PATENT APPLICATION
ASST. COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

Sir:

This is a request for filing a ☒ continuation ☐ divisional application under 37 CFR 1.60, of pending prior application Serial No. 08/433,423 filed on July 3, 1995 (date) of Christopher R. Parish (inventor currently of record in prior application)

for ANGIOGENESIS INHIBITORY ANTIBODIES (title of invention)

1. ☒ Enclosed is a copy of the prior application, including an oath or declaration as originally filed and an affidavit or declaration verifying it as a true copy. (See 7 and 7a for drawing requirements.)

2. ☒ The filing fee is calculated below.

CLAIMS	(1) FOR	(2) NUMBER FILED	(3) NUMBER EXTRA	(4) RATE	(5) CALCULATIONS
	TOTAL CLAIMS	1 -20 =	0	X $ 22 =	$ 0
	INDEPENDENT CLAIMS	1 -3 =	0	X $ 82 =	$ 0
	MULTIPLE DEPENDENT CLAIM(S) (IF APPLICABLE)			X $260 =	
				BASIC FEE	$ 770.00
				TOTAL OF ABOVE CALCULATIONS	$ 770.00
	Reduction by ½ for filing by small entity (Note 37 C.F.R. 1.9, 1.27, 128). If applicable, verified statement must be attached.				$ 385.00
				TOTAL	$ 385.00

☒ Verified Statement of Small Entity Established in Parent Case

3. ☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any

overpayment, to Deposit Account No. 06-2425. A duplicate copy of this sheet is enclosed.

4. ☒ A check in the amount of $385.00 is enclosed.

5. ☒ Cancel in this application original claims 2-16 of the prior application before calculating the filing fee. (At least one original independent claim must be retained for filing purposes.)

6. ☒ Amend the specification by inserting before the first line the sentence: -This is a ☒ continuation, ☐ division, of application Serial No. 08/433,423, filed July 3, 1995 _____.

7. ☐ Transfer the drawings from the prior application and abandon said prior application as of the filing date accorded this application. A duplicate copy of this sheet is enclosed for filing in the prior application file. (May only be used if signed by person authorized by §1.138 and before payment of issue fee.)

7a. ☒ New formal/informal drawings are enclosed.

7b. ☒ Priority of application Serial No. PL5573 filed on 29 October 1992 in Australia and Serial No. PCT/AU93/00558 filed on 29 October 1993 in the PCT is claimed under 35 U.S.C. 119 or 35 U.S.C. 365(a). (foreign priority or international)

7c. ☐ The certified copy has been filed in prior application Serial No. _____, filed _____.

8. ☒ The prior application is assigned of record to THE AUSTRALIA NATIONAL UNIVERSITY.

9. ☒ The power of attorney in the prior application is to CRAIG B. BAILEY, Reg. No. 28,786; JAMES W. PAUL, Reg. No. 29,967; GILBERT G. KOVELMAN, Reg. No. 19,552; JOHN S. NAGY, Reg. No. 30,664 and DAVID G. PARKHURST, Reg. No. 29,422

all of FULWIDER PATTON LEE & UTECHT, LLP
10877 Wilshire Bouelvard
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Los Angeles, CA 90024

a. ☐ The power appears in the original papers in the prior application

b. ☒ Since the power does not appear in the original papers, a copy of the power in the prior application is enclosed.

c. ☒ Address all future communications to Craig B. Bailey, Esq. . (May only be complete by applicant, or attorney or agent of record)

10. ☒ A preliminary amendment is enclosed. (Claims added by this Amendment have been properly numbered consecutively beginning with the number next following the highest numbered original claim in the prior application.)

11. ☒ I hereby verify that the attached papers are a true copy of prior application Serial No. 08/433,423 as originally filed on July 3, 1995.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

March 13, 1997

David G. Parkhurst, Reg. No. 29,422

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☐ Inventor(s)
☐ Assignee of complete interest
☒ Attorney or agent of record
☐ Filed under § 1.34(a)

ANGIOGENESIS INHIBITORY ANTIBODIES

FIELD OF THE INVENTION

This invention relates to angiogenesis inhibitory antibodies, and to the use thereof in the inhibition of angiogenesis, particularly angiogenesis associated with the growth of solid tumours, with proliferative retinopathies, and with certain inflammatory diseases.

BACKGROUND TO THE INVENTION

The circulatory system represents an extensive, branching, network of blood vessels which is essential for the supply of oxygen and nutrients to tissues and for the removal of byproducts of metabolism. In adults the development of new blood vessels or "angiogenesis" rarely occurs except during wound healing or as a result of a number of pathological situations termed "angiogenesis-dependent diseases"[1,2]. The most important of these is the angiogenesis associated with the growth of solid tumours and with proliferative retinopathies. Angiogenesis may also play an important role in rheumatoid arthritis and psoriasis.

Angiogenesis inhibitors can, therefore, be of considerable value in the treatment of angiogenesis-dependent diseases. For example, in the case of solid tumours, the development of a blood supply is essential for the growth and survival of the tumour. Thus, inhibition of angiogenesis can provide a highly selective means of inducing tumour regression. Similarly, angiogenesis inhibitors may be used to prevent the blindness associated with proliferative diabetic retinopathy, one of the major complications of diabetes.

In work leading to the present invention, monoclonal antibodies (mAbs) have been developed against proliferating/angiogenic human endothelial cells which can be used either to directly inhibit angiogenesis or to target cytotoxic drugs or radioisotope labels to sites of angiogenesis. Since angiogenesis does

not occur in adults, except following tissue injury, such mAbs can be remarkably specific. Furthermore, unlike other lines of research which have produced cancer cell-specific mAbs to target cytotoxic drugs to tumours, the present invention is directed to producing mAbs against host antigens. This approach has the major advantage that generation of "resistant" variants of the tumour cannot occur and, in theory, one mAb could be used to treat all solid tumours. An additional advantage is that endothelial cells, by virtue of their vascular location, are very accessible to mAbs in the circulation.

SUMMARY OF THE INVENTION

According to the present invention, there are provided antibodies, including monoclonal antibodies, specific for proliferating/angiogenic human endothelial cells.

More particularly, the present invention provides antibodies, including monoclonal antibodies, specific for proliferating/angiogenic human umbilical vein endothelial cells (HUVEC) or human umbilical artery endothelial cells (HUAEC).

This invention also extends to hybridoma cell lines producing the monoclonal antibodies as described above, which may be produced by methods well known to persons skilled in this field.

As previously described, the antibodies in accordance with the invention may be used alone as an anti-angiogenesis agent in the treatment of angiogenesis-dependent disease in a patient.

In another aspect, the present invention provides an antibody-conjugate comprising an antibody specific for proliferating/angiogenic human endothelial cells, having a toxin material or label conjugated thereto.

The toxin material may, for example, be a cytotoxic drug or other cytotoxic material, however other toxin materials well known to persons skilled in this art

may also be incorporated in the antibody-conjugate of this aspect of the invention. The label may be a radioisotope. Suitable toxin materials include, by way of example, ricin A chain, diphtheria toxin, Pseudomonas exotoxin A and idarubicin. A suitable radiolabel is technetium -99m. Coupling of various toxins to monoclonal antibodies may be effected by known methods[3,4,5,6]. Similarly, the preparation of a conjugate with a radiolabel may use known methods[7].

In yet another aspect, the invention provides a composition, particularly a therapeutic composition for inhibition of angiogenesis or for treatment of angiogenesis-dependent disease, comprising an antibody or antibody-conjugate as broadly described above, together with a pharmaceutically acceptable carrier or diluent.

The present invention also extends to a method for inhibition of angiogenesis in a patient, for example angiogenesis associated with the growth of solid tumours or with proliferative retinopathies, which comprises administration to said patient of an inhibition-effective amount of an antibody or antibody-conjugate as broadly described above.

In another aspect, this invention provides a method for treatment of angiogenesis-dependent disease in a patient, which comprises administration to said patient of a therapeutic-effective amount of an antibody or antibody-conjugate as broadly described above.

Administration of the antibody or antibody-conjugate may be by any suitable route. Preferably, the administration to the patient is parenterally, for example, by injection.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with one embodiment of this invention, there have been developed monoclonal antibodies (mAbs) specific for proliferating/angiogenic endothelial cells. The major use of these mAbs is to simply inhibit angiogenesis,

although if desired the mAbs can be used to target cytotoxic drugs or labels to angiogenic sites. In the case of tumours, this approach has the major advantages of tumour specificity, minimal side-effects, and little chance of "resistant" tumour variants arising. Furthermore, these mAbs provide a single therapeutic agent that can be used for all solid tumours, regardless of type and tissue location, and inhibition of angiogenesis in the solid tumours can result in tumour regression.

The initial experimental approach has been to raise murine mAbs against proliferating/angiogenic human umbilical vein endothelial cells (HUVEC). Resultant mAbs have been screened initially for HUVEC reactivity and, subsequently, mAbs have been eliminated which react with other human cell lines, e.g. human melanoma cell lines. Finally, endothelial specific mAbs have been identified which fail to react with freshly isolated, non-proliferating/non-angiogenic human endothelial cells. Using this approach, it has been clearly established that mAbs can be obtained which are specific for proliferating/angiogenic human endothelial cells.

BRIEF DESCRIPTION OF THE DRAWING

Figure 1 shows binding of mAbs to proliferating/angiogenic and resting (non-proliferating/non-angiogenic) human umbilical vein endothelial cells (HUVEC) as detected by immunofluorescence flow cytometry. CONT refers to HUVEC not incubated with mAbs, 20G5 is a HUVEC-specific mAb which reacts with both proliferating/angiogenic and resting HUVEC and 9B11 is a HUVEC-specific mAb which only reacts with proliferating/angiogenic HUVEC.

Further details of the present invention will be apparent from the following detailed description of the production of endothelial specific mAbs in accordance with the invention.

EXAMPLE

A. Materials and Methods

Cells

Human umbilical vein (HUVEC) and artery (HUAEC) endothelial cells were prepared from human umbilical cords by the method of Jaffe[8] and cultured in Medium 199 supplemented with 20% foetal calf serum (FCS), L-glutamine, antibiotics, 130 ug/ml heparin and 1.2 mg/ml endothelial cell growth supplement (Sigma). HUVEC were used for mAb binding studies between passages 2 and 7. Human tumour cell lines (e.g. MM-170 melanoma, K562 erythroleukaemia) were cultured in RPMI-1640/10% FCS. Mononuclear cells (lymphocytes and monocytes) and neutrophils were simultaneously isolated from human peripheral blood by centrifugation of diluted blood on Polymorphprep™ (Nycomed. Pharma A.S., Oslo, Norway). Red cells and platelets were isolated by differential centrifugation from citrated human blood.

Production of Hybridomas

BALB/c mice were immunised, i.p., 3-4 times at 2-4 weekly intervals with $15x10^6$ HUVEC in PBS and challenged 3 days prior to spleen cell removal with $15x10^6$ HUVEC. A spleen cell suspension was prepared, fused with the myeloma NS1/1.AG4.1 and hybridomas grown up and cloned as described previously[9]. To improve hybridoma growth and cloning efficiencies 10% endothelial cell conditioned medium (HUVEC or bovine corneal EC) was included in culture media.

mAb Screening Assays.

Initially hybridoma culture supernatants were tested for reactivity with HUVEC by immunofluorescence flow cytometry. Briefly, HUVEC ($5x10^4$) were incubated (30 min, 4°C) with undiluted hybridoma supernatant, washed and incubated with FITC-sheep $F(ab')_2$ anti-mouse Ig(100µg/ml). Following final washing HUVEC were examined for mAb binding by analysis on a Becton-Dickinson FACScan. Positive hybridoma supernatants were then screened on the human melanoma cell line MM-170 to eliminate non-endothelial specific mAbs.

Endothelial specificity was further confirmed by screening mAbs on a panel of human tumour cell lines and human lymphocytes, monocytes, neutrophils, red cells and platelets. Finally, specificity for proliferating HUVEC was established by screening hybridoma supernatants on freshly isolated (non-cultured) HUVEC. Hybridomas which were positive on proliferating HUVEC but negative on freshly isolated HUVEC were cloned[9] for further study. A number of hybridomas (e.g. 20G5) which were endothelial-specific but not proliferation/angiogenesis-specific were also cloned.

HUVEC Proliferation Assay

Assays were performed in 96 well, flat bottom, microplates coated with 0.1% gelatin and containing $2.5x10^4$ HUVEC/well in 150µl of culture medium. After 24hr culture cells were pulsed with ^{3}H-thymidine for a further 24hr and ^{3}H-thymidine incorporation assessed in washed and harvested cells using a Titertek 530 cell harvester (Flow Labs). In mAb blocking experiments 50 µl/well of hybridoma supernatant was added at the commencement of the cultures with supernatant from a hybridoma which does not react with HUVEC being used as a negative control.

B. Results

Production of mAbs Specific for Proliferating/Angiogenic Endothelial Cells

Table 1 shows that mAbs can be obtained which are specific for proliferating/angiogenic human endothelial cells.

TABLE 1 Production of Endothelial Specific Monoclonal Antibodies (mAbs).

Hybridomas	Number	
	Fusion #1	Fusion #2
Total screened	1196	660
Proliferating HUVEC positive	811	276
Proliferating HUVEC specific	541[a]	102[b]
Non-proliferating (resting) HUVEC negative	25[c]	17[c]

a Hybridomas not reactive with the human melanoma cell line MM-170.

b Hybridomas not reactive with human MM170 cell line, U937 monocytic cell line, lymphocytes, neutrophils, monocytes, red cells and platelets.

c Hybridomas not reactive with endothelial cells freshly isolated from the human umbilical cord, i.e. endothelial cells "non-proliferating" or "resting".

HUVEC = Human umbilical vein endothelial cells.

In the first fusion of 1196 hybridomas screened, 811 reacted with proliferating/angiogenic endothelial cells of which 541 were proliferating/angiogenic endothelial cell specific, i.e. failed to react with other proliferating human cell lines such as the human melanoma line MM-170. Of particular importance was the fact that 25 of the 541 hybridomas specific for proliferating/angiogenic human endothelial cells failed to react with non-proliferating/non-angiogenic (freshly isolated) endothelial cells. Thus, 4.6% of hybridomas produce mAbs which are proliferation/angiogenesis specific, a clear validation of the approach being used. A similar result was obtained in a second fusion where 16.6% of the HUVEC-specific mAbs were angiogenesis specific. A typical example of the results obtained with a proliferation/angiogenesis-specific (9B11) and a proliferation/angiogenesis non-specific (20G5) mAb is depicted in Fig.1 as revealed by immunofluorescence flow cytometry.

Table 2. **Reactivity Pattern of Some Cloned Monoclonal Antibodies Against Human Endothelial Cells**

Human Cells	mAb Clones					
	9D9 (IgM)	12E5 (IgM)	10A5 (IgM)	14G11 (IgG1)	21F10 (IgM)	20G5 (IgM)
Proliferating HUVEC	+	+	+	+	+	+
Resting HUVEC	-	-	-	-	-	+
Proliferating HUAEC	+	+	+	+	+	+
K562 erythroleukaemia	-	-	+	+	+	-
MM170 melanoma	-	±	+	+	+	-
PE.01 ovarian carcinoma	-	-	+	+	+	-
COLO397 colonic carcinoma	-	-	+	+	+	-
KJD keratinocyte carcinoma	-	-	+	+	+	-
MT2 B lymphoma	-	-	+	+	+	+
Molt 4 T lymphoma	-	-	+	+	+	+
U937 (monocytic)	-	-	+	+	+	-
Lymphocytes	-	-	+	-	-	+
Neutrophils	-	±	±	-	-	+
Monocytes	-	+	+	±	-	+
RBC	-	-	-	-	-	-
Platelets	±	-	±	+	-	+
Fibroblasts	-	-	-	±	-	-

HUVEC = human umbilical vein endothelial cells.
HUAEC = human umbilical artery endothelial cells.

Table 2 presents detailed specificity analysis of six cloned mAbs, which were HUVEC reactive, as examples. One mAb (20G5) is a control which reacts with both resting and proliferating/angiogenic endothelial cells and is probably specific for the CD31 antigen. The remaining five mAbs react with proliferating/angiogenic but not resting endothelial cells. Three of these mAbs (10A5, 14G11, 21F10) react with many other proliferating cell types. The remaining two clones (9D9 and 12E5) exhibit considerable specificity for proliferating/angiogenic endothelial cells, 9D9 being the mAb with the greatest specificity, only exhibiting a weak reaction with platelets.

The 9D9 mAb reacts with proliferating/angiogenic venular or arterial endothelial cells but not non-proliferating (resting) endothelial cells (Table 2). Subsequent studies showed that the 9D9 antigen appears on cultured HUVECS within 24 hr of culture and persists on HUVEC cultured for many passages, i.e. ten passages over a period of two months. The 9D9 antigen also appears on HUVEC whether they are cultured in 20% FCS + bovine growth supplement or 20% human serum, indicating that the 9D9 antigen is not derived from culture medium components.

Effect of mAbs on Endothelial Cell Proliferation.

When some of the proliferation-specific mAbs were added to proliferating HUVEC *in vitro* it was found that some of the mAbs could directly inhibit HUVEC proliferation. The results of a typical experiment are present in Table 3.

TABLE 3 Inhibition of HUVEC Proliferation by mAbs Specific for Proliferating/Angiogenic Endothelial Cells.

mAb	Specificity	^{3}H-Thymidine Incorporation* (cpm)	Response % Control
9B9	Non-reactive	7779±1420	100
20G5	HUVEC	6806±1290	87.5
1D5	Proliferating HUVEC**	1256±110	16.1
8G4	Proliferating HUVEC**	1857±38	23.9
16C6	Proliferating HUVEC**	1767±175	22.7
19D4	Proliferating HUVEC**	7530±753	96.8

* HUVEC cultured in proliferation assay with dialyzed hybridoma supernatants containing mAbs. Proliferation measured 24-48 hr following culture initiation and represents mean ± standard error of three determinations.

** mAbs only react with proliferating/angiogenic (not resting) HUVEC.

Of the four proliferation/angiogenesis-specific mAbs tested, three (1D5, 8G4 and 16C6) inhibited HUVEC proliferation by approx. 75-85% as measured by ^{3}H-thymidine incorporation. In contrast, one proliferation/angiogenesis-specific mAb (19D4) and 20G5, a mAb which reacts with both proliferating and non-proliferating HUVEC, had no significant effect on HUVEC proliferation. The mAb 9B9, which does not react with HUVEC, was used as the negative control in this experiment.

These data strongly suggest that some of the proliferation/angiogenesis-specific mAbs may directly inhibit angiogenesis, thus bypassing the need for cytotoxic drug-mAb conjugates. It should be emphasised that the data presented in Table 2 were obtained with hybridoma supernatants and not with purified and concentrated mAb preparations.

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6. Pietersz, G.A., Smyth, M.J. and McKenzie, I.F.C. *Cancer Res.* 48, 926-931 (1988).

7. Lee, R-T., Milner, L.J., Boniface, G.R., Bautovich, G.J., Weedon, A.R.J., Bundesen, P.G., Rylatt, D.B. and Walker, K.Z. *Immunol. Cell Biol.* 70, 173-179 (1992).

8. Jaffe, E.A. In "*Biology of Endothelial Cells*", E.A. Jaffe, ed., Martinus-Nijhoff, The Hague (1984).

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CLAIMS:

1. An antibody specific for proliferating/angiogenic human endothelial cells.

2. An antibody according to claim 1 which is specific for proliferating/angiogenic human umbilical vein endothelial cells (HUVEC) or human umbilical artery endothelial cells (HUAEC).

3. An antibody according to claim 1 or claim 2 which is a monoclonal antibody.

4. A hybridoma cell line producing a monoclonal antibody according to claim 3.

5. An antibody-conjugate comprising an antibody specific for proliferating/angiogenic human endothelial cells, having a toxin material or label conjugated thereto.

6. An antibody-conjugate according to claim 5, wherein said antibody is specific for proliferating/angiogenic human umbilical vein endothelial cells (HUVEC) or human umbilical artery endothelial cells (HUAEC).

7. An antibody-conjugate according to claim 5 or claim 6, wherein said antibody is a monoclonal antibody.

8. An antibody-conjugate according to claim 5, wherein said antibody is conjugated to a cytotoxic material.

9. An antibody-conjugate according to claim 8, wherein said cytotoxic material is ricin A chain, diphtheria toxin, Pseudomonas exotoxin A or idarubicin.

10. An antibody-conjugate according to claim 5, wherein said antibody is conjugated to a radioisotope label.

11. An antibody-conjugate according to claim 10, wherein said radioisotope label is technetium-99m.

12. A therapeutic composition for inhibition of angiogenesis or for treatment of angiogenesis-dependent disease, comprising an antibody according to any of claims 1 to 3 or an antibody-conjugate according to any of claims 5 to 11, together with a pharmaceutically acceptable carrier or diluent.

13. A method for inhibition of angiogenesis in a patient, including angiogenesis associated with the growth of solid tumours or with proliferative retinopathies, which comprises administration to said patient of an inhibition-effective amount of an antibody according to any of claims 1 to 3 or an antibody-conjugate according to any of claims 5 to 11.

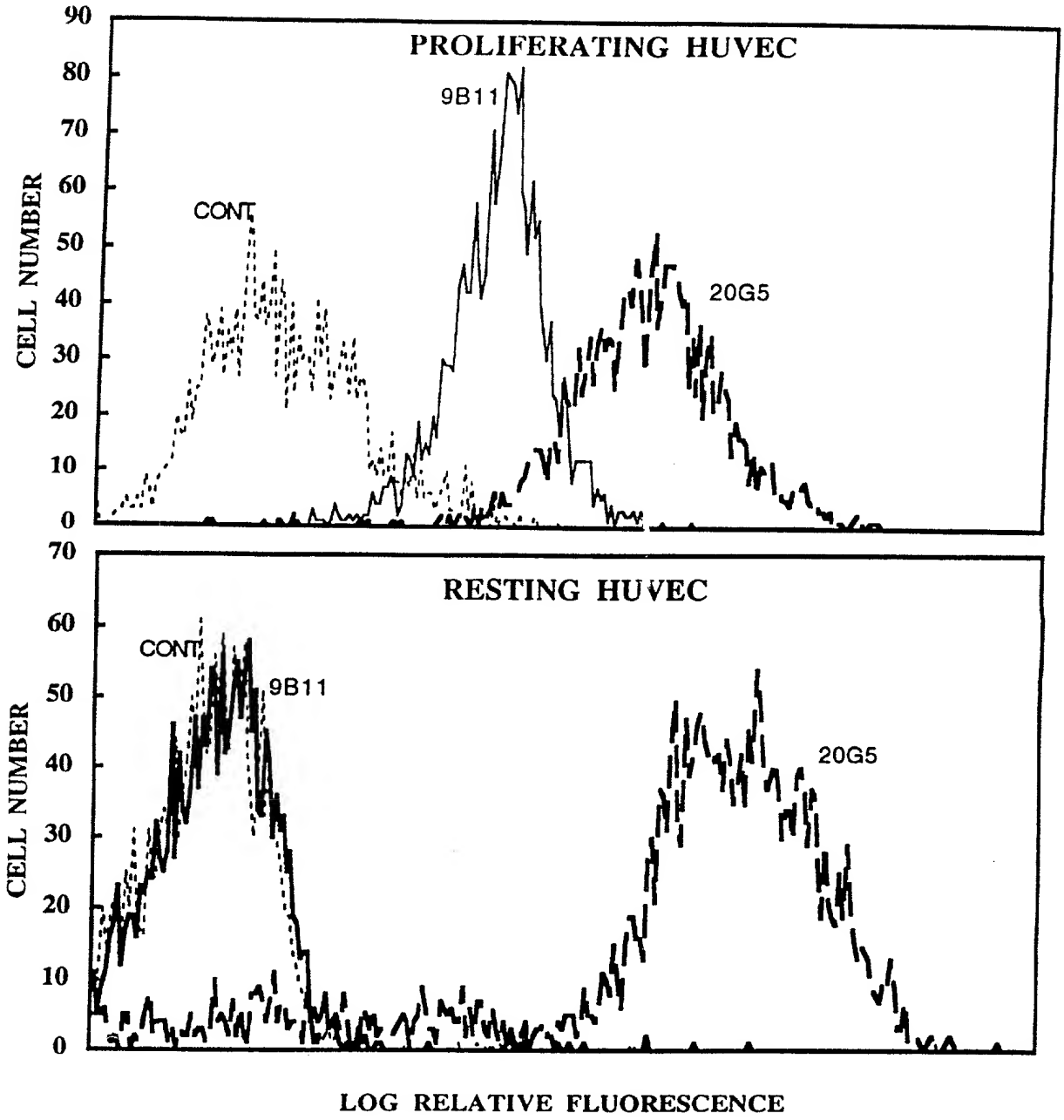
14. Use of an antibody according to any of claims 1 to 3 or an antibody-conjugate according to any of claims 5 to 11, in the manufacture of a pharmaceutical composition for inhibition of angiogenesis in a patient, including angiogenesis associated with the growth of solid tumours or with proliferative retinopathies.

15. A method for treatment of angiogenesis-dependent disease in a patient, which comprises administration to said patient of a therapeutic-effective amount of an antibody according to any of claims 1 to 3 or an antibody-conjugate according to any of claims 5 to 11.

16. Use of an antibody according to any of claims 1 to 3 or an antibody-conjugate according to any of claims 5 to 11, in the manufacture of a pharmaceutical composition for treatment of angiogenesis-dependent disease.

ABSTRACT OF THE DISCLOSURE

Antibodies, including monoclonal antibodies, specific for proliferating/angiogenic human endothelial cells such as human umbilical vein endothelial cells and human umbilical artery endothelial cells, and conjugates of these antibodies with a toxin material or label, are useful for inhibition of angiogenesis or for treatment of angiogenesis-dependent disease.


PROLIFERATING HUVEC
9B11
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RESTING HUVEC
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LOG RELATIVE FLUORESCENCE

Figure 1

DECLARATION AND POWER OF ATTORNEY
FOR PATENT APPLICATION

As the below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original and first inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled ANGIOGENESIS INHIBITORY ANTIBODIES, the specification of which (check one)

_____ is attached hereto
___X___ was filed on April 28, 1995
Application Serial No. 08/433,423
and was amended on (or amended through) April 28, 1995

(if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, Sec. 1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, Sec. 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed	
PL5573	Australia	29 October 1992	X	___
No.	Country	Day/Month/Year filed	Yes	No
PCT/AU93/00558	PCT	29 October 1993	X	___
No.	Country	Day/Month/Year filed	Yes	No

I hereby claim the benefit under Title 35, United States Code, Sec. 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Sec. 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Sec 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application.

Appln. Serial No.	Filing Date	Status (patented, pending abandoned)
NONE		

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I hereby appoint the following attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

CRAIG B. BAILEY, Registration No. 28,786,
JAMES W. PAUL, Registration No. 29,967,
GILBERT G. KOVELMAN, Registration No. 19,552,
JOHN S. NAGY, Registration No. 30,664, and
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Serial or Patent No.: 08/[illegible],423
Filed or Issued: 28 April 1995
For: ANGIOGENESIS INHIBITORY ANTIBODIES

Attorney's Docket No: 37188

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS
(37 CFR 1.9(f) and 1.27(d)) - NONPROFIT ORGANIZATION

I hereby declare that I am an official empowered to act on behalf of the nonprofit organization identified below:

NAME OF ORGANIZATION THE AUSTRALIAN NATIONAL UNIVERSITY
ADDRESS OF ORGANIZATION Acton, Australian Capital Territory, 2601, Australia

TYPE OF ORGANIZATION

[X] UNIVERSITY OR OTHER INSTITUTION OF HIGHER EDUCATION
[ ] TAX EXEMPT UNDER INTERNAL REVENUE SERVICE CODE (26 USC 501(a) and 501(c)(3))
[ ] NONPROFIT SCIENTIFIC OR EDUCATIONAL UNDER STATUTE OF STATE OF THE UNITED STATES OF AMERICA
(NAME OF STATE _____)
(CITATION OF STATUTE _____)
[ ] WOULD QUALIFY AS TAX EXEMPT UNDER INTERNAL REVENUE SERVICE CODE (26 USC 501(a) and 501(c)(3)) IF LOCATED IN THE UNITED STATES OF AMERICA
[ ] WOULD QUALIFY AS NONPROFIT SCIENTIFIC OR EDUCATIONAL UNDER STATUTE OF STATE OF THE UNITED STATES OF AMERICA IF LOCATED IN THE UNITED STATES OF AMERICA
(NAME OF STATE _____)
(CITATION OF STATUTE _____)

I hereby declare that the nonprofit organization identified above qualifies as a nonprofit organization as defined in 37 CFR 1.9(e) for purposes of paying reduced fees under section 41(a) or (b) of Title 35, United States Code with regard to the invention entitled ANGIOGENESIS INHIBITORY ANTIBODIES by inventor(s) Christopher Richard PARISH described in

[ ] the specification filed herewith
[X] application serial no. 08.433,423, filed 28 April 1995
[ ] patent no. _____, issued _____.

I hereby declare that rights under contract or law have been conveyed to and remain with the nonprofit organization with regard to the above identified invention.

If the rights held by the nonprofit organization are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who could not qualify as a small business concern under 37 CFR 1.9(d) or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e). *NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

NAME _____
ADDRESS _____
[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

NAME _____
ADDRESS _____
[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING Millicent Eleanor POOLE
TITLE IN ORGANIZATION Deputy Vice-Chancellor
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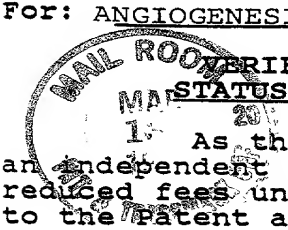
SIGNATURE M E Poole DATE 6 6 95

Applicant or Patentee: Christopher R. Parish
Serial or Patent No: 08/433,423
Filed or Issued: April 28, 1995
For: ANGIOGENESIS INHIBITORY ANTIBODIES

Attorney's Docket No. 37188



VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(f) AND 1.27(b)) - INDEPENDENT INVENTOR

As the below named inventor, I hereby declare that I qualify as an independent inventor as defined in 37 CFR 1.9(c) for purposes of paying reduced fees under Section 41(a) and (b) of Title 35, United States Code, to the Patent and Trademark Office with regard to the invention entitled: ANGIOGENESIS INHIBITORY ANTIBODIES described in

[ ] the specification filed herewith
[x] application Serial No. 08/433,423 filed April 28, 1995
[ ] Patent No. _____, issued _____

I have not assigned, granted, conveyed or licensed and am under no obligation under contract or law to assign, grant, convey or license, any rights in the invention to any person who could not be classified as an independent inventor under 37 CFR 1.9(c) if that person had made the invention, or to any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

Each person, concern, or organization to which I have assigned, granted, conveyed, or licensed or am under or may be under an obligation under contract or law to assign, grant, convey, or license any rights in invention is listed below:

[ ] no such person, concern, or organization
[x] persons, concerns or organizations listed below *

* Note: Separate verified statements are required for each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

Full Name: The Australian National University
Address: Acton, Australian Capital Territory 2601
Australia

[ ] Individual [ ] Small Business Concern [x] Nonprofit Organization

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Name of Inventor: Christopher R. Parish

Signature of Inventor: C.R. Parish

Date: 16 June, 1995